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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,955	07/11/2001	Gabriel Stavros Panayi	78104.023	2246

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DeWitt Ross & Stevens
Firstar Financial Centre
Suite 401
8000 Excelsior Drive
Madison, WI 53717-1914

EXAMINER	
JAMROZ, MARGARET E	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 02/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,955	PANAYI ET AL.	
	Examiner	Art Unit	
	Margaret E Jamroz	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-53* is/are pending in the application.

4a) Of the above claim(s) *20,21 and 26-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,22-25, and 44-53* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 18-53 are pending.

Applicant's election with traverse of Group I (claims 18, 19, 22-25, and 44-53 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that applicant argues that all of the subject claims do relate to a single inventive concept and that the Office has not proved a burden of search. Further, applicant argues that the documents do not teach the amino acid sequence recitation for the proteins described therein. This is not found persuasive because claims 18 and 22-23 do not recite SEQ ID NOS, and therefore, the references cited in Paper No: 8 comprising recombinant immunoglobulin heavy chain binding proteins anticipate the claimed invention; therefore, the claims do not define a contribution of a special technical feature over the prior art according to 37 CFR 1.475 (see MPEP 1850). The restriction of Groups II, III, IV, and VI is maintained as they relate to DNA, a method for treating inflammation, a pharmaceutical composition comprising DNA, and a method of diagnosis are therefore not linked to form a single general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-21 and 26-43 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.

Claims 18-19, 22-25, and 44-53 are under consideration in the instant application.

2. The specification is objected under 37 CFR 1.821(d) for failing to disclose SEQ ID NOS, for example, pages 8 and 23-26 and the claims, as appropriate to reflect compliance with the Sequence Rules.

Appropriate correction is required.

3. Applicant should amend the first sentence of the specification to indicate priority is claimed under 35 U.S.C. 371 to PCT/GB99/03316 (37 CFR 1.78).

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The disclosure is objected to because of the following informalities: "SE" on page 2, lines 7-9 of the specification should be "SEQ ID NO: 1, 2, or 3"; "prolifeation" on page 13, final paragraph, should be "proliferation"; on page 15, lines 2 and 4, "p" should be followed by a numeric value. On page 14, final paragraph, page 15, first paragraph, applicant refers to Figures 4 and 6, however, applicant has only submitted Figures 1-3.

Appropriate correction is required.

6. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-Reference to Related Applications.

(c) Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).

(e) Background of the Invention.

1. Field of the Invention.
2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(i) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

7. Claim 18 is objected to because of the following informalities: A claim should be a complete sentence and should start with "A". Appropriate correction is required.

8. Claim 22 is objected to because of the following informalities: line 3 should read "amount of **an** immunoglobulin". Appropriate correction is required.

9. Claim 23 is objected to because of the following informalities: line 2 should read "protein is **a** recombinant". Appropriate correction is required.

10. Claims 46-47, 49, and 52 are objected to because of the following informalities: line 1 should read "**a** recombinant". Appropriate correction is required.

11. Claim 48 is objected to because of the following informalities: line 2 should read "incorporates **said** immunoglobulin". Appropriate correction is required.

12. Claim 51 is objected to because of the following informalities: line 2 should read "**said** immunoglobulin". Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 18, 22-25, and 44-53 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant immunoglobulin heavy chain binding protein comprising SEQ ID NOS: 1 and 2 (human p78), SEQ ID NOS: 1 and 2 in a pharmaceutically acceptable excipient, and a kit for the detection of SEQ ID NOS 1 and 2 *in vitro*, comprising an ELISA or Western Blot, does not reasonably provide enablement for the genus of recombinant immunoglobulin heavy chain binding proteins or peptides thereof as compounds, a pharmaceutical composition for the treatment of any inflammation in mammals comprising any immunoglobulin heavy chain binding protein, or any kit for the diagnosis of the presence of rheumatoid arthritis in a mammalian subject comprising any immunoglobulin heavy chain binding protein, or any peptide thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant disclosed on page 12, first paragraph, that "collagen arthritis (CIA) and pristine arthritis (PIA) were induced in DBA/1 mice according to our previously described protocol", however, applicant did not describe the protocol or provide a citation for a publication to describe induction of said arthritis models. Applicant further discloses that anti-p78 antibody titers were measured by ELISA. However, applicant does not disclose the administration of type II collagen in CFA to the mice to induce arthritis or measure the clinical score of the disease. Therefore, one of skill in the art would not be convinced that arthritis was indeed induced. Further, on page 14 of the specification, applicant discloses that immunization of DBA/1 mice with p78 in CFA did not lead to the development of arthritis, however, in the absence of type II collagen immunization, arthritis would not be induced in the DBA/1 mice; therefore, it is of no surprise that arthritis was not induced following immunization with p78/CFA alone. Consequently, the anti-p78 antibodies detected would not have been developed at the onset of arthritis as stated in the final line, because arthritis had not been induced. On page 15, applicant discloses a method of "preventing" CIA wherein mice were immunized with p78 or PBS followed by CII/CFA one week later; anti-CII IgG antibodies were decreased in mice pre-treated with p78.

Malfait et al. (Journal of Immunology 1999 May; 162(10: 6278-6283) teach that Male DBA/1 mice were immunized with CII emulsified in CFA by intradermal injection; mice were examined for paw swelling and clinical score after day 15. Treatment of the disease commenced at the onset of disease and a group of mice were injected with PBS alone (see the Materials and Methods on pages 6278-9 in particular). Further, Geiger et al. (Journal of Rheumatology 1994 Nov; 21(11): 1992-1997) teach CIA induced in DBA/1 mice by intradermal injection of CII in CFA on day 0; and the drug of interest was applied orally 5 times/week starting at day 15 after immunization (e.g. after onset of disease symptoms) and anticollagen antibody titers were determined (see the Abstract, Materials and Methods, and Figure 5 in particular). Arthritis cannot be induced in DBA/1 mice in the absence of CII injection; therefore, one of ordinary skill in the art would not be enabled to practice the claimed invention within the scope of using SEQ ID NOS 1 and 2 in a pharmaceutical composition for the treatment of any inflammation in any mammal comprising any immunoglobulin heavy chain binding protein, or peptide thereof; or any kit comprising any immunoglobulin heavy chain for diagnosing the presence of rheumatoid arthritis in any mammalian subject.

Arthritis is not a predictable disease, therefore; treatment cannot commence prior to the onset of disease symptoms. Consequently, applicant's disclosure that injection of p78 prior to induction of CII and onset of disease symptoms is not an accurate measurement of the efficacy of p78 in "treating" arthritis or any other type of inflammation, and in the absence of induction of arthritis, applicant has not shown "prevention" of arthritis or any other type of inflammation.

Therefore, applicant has not disclosed any method of treating any inflammation with any immunoglobulin heavy chain binding protein. Further, in the absence of Figure, 6, one of skill in the art cannot refer to the histology of the joints, and applicant has not taught any method of "treating" any inflammatory condition in any mammal.

Consequently, applicant has not disclosed any working examples of any pharmaceutical composition comprising any immunoglobulin heavy chain binding protein (recombinant or otherwise) for the treatment of any inflammation in any mammal or any methods of treating any inflammatory disease (including arthritis) comprising administering any immunoglobulin heavy chain binding protein (recombinant or otherwise). Applicant is only enabled for a pharmaceutical composition comprising SEQ ID NOS: 1 and 2 for the *in vivo* production of antibodies in mice.

The claims as written encompass a kit comprising any immunoglobulin heavy chain binding protein (recombinant or otherwise), however; applicant's disclosure on pages 12-13 and ELISA to detect SEQ ID NOS: 1 and 2; and on page 15, a Western Blot enables applicant for only for a kit for the detection of SEQ ID NOS: 1 and 2 by ELISA or Western.

Applicant is relying upon certain biological activities and the disclosure of two human sequences of immunoglobulin heavy chain binding proteins to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated amino acid sequences having or encoding any recombinant immunoglubulin heavy chain binding proteins or peptide thereof encompassed by the claimed invention other than "proteins set forth by SEQ ID NOS: 1 and 2" would be expected to have greater differences in their activities.

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of recombinant immunoglubulin heavy chain binding proteins, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional recombinant immunoglubulin heavy chain binding proteins with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it

would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

Further, applicant has shown a single instance of decreased anti-collagen antibodies and clinical score of arthritis in Tables 2-3 by pre-treating DBA/1 mice with SEQ ID NOS: 1 and 2. However, applicant has not shown any working examples of any pharmaceutical composition for treating any inflammatory disease comprising administering any recombinant immunoglubulin heavy chain binding protein, or any kit for the diagnosis of rheumatoid arthritis in any mammalian subject comprising any immunoglobulin heavy chain binding protein, or peptide thereof.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

15. Claims 18, 22-25, and 44-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of SEQ ID NOS: 1 and 2, which are human p78, SEQ ID NOS: 1 and 2 in a pharmaceutically acceptable excipient, and a kit for the detection of SEQ ID NOS 1 and 2 *in vitro*, comprising an ELISA or Western Blot.

Applicant is not in possession of any other species of p78, any peptides thereof, or any kit for the diagnosis of the presence of rheumatoid arthritis in a mammalian subject comprising any immunoglobulin heavy chain binding protein, or any peptide thereof.

Applicant has disclosed SEQ ID NOS: 1 and 2 which are both drawn to a single species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant

claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

The specification fails to define the genus p78. The claims as written encompass the genus immunoglobulin heavy chain binding proteins, and peptides thereof. Therefore, the skilled artisan cannot envision all the contemplated immunoglobulin heavy chain binding proteins, and peptides thereof, possibilities recited in the instant claims. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

17. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Ting et al., of record, P11021, of record, Witzmann et al., of record, or Haas et al., of record.

Ting et al. teach a recombinant human gene encoding the 78-000-Dalton Glucose-related Protein and Its Pseudogene: Structure, Conservation, and Regulation; which is a recombinant immunoglobulin heavy chain binding protein. The amino acid sequence SEQ ID NO: 2 of the instant application is 98% identical to the protein taught be the references and differs only in that the first and last amino acid residues of SEQ ID NO: 2 differ from the reference sequence.

P11021 teaches a recombinant human gene encoding the 78-000-Dalton Glucose-related Protein and Its Pseudogene: Structure, Conservation, and Regulation; a recombinant immunoglobulin heavy chain binding protein. The amino acid sequence SEQ ID NO: 2 of the instant application is 98% identical to the protein taught be the references and differs only in that the first and last amino acid residues of SEQ ID NO: 2 differ from the reference sequence.

Witzmann et al. teach recombinant BiP, which is a recombinant immunoglobulin heavy chain binding protein (see the entire document).

Haas et al. teach recombinant BiP, which is a recombinant immunoglobulin heavy chain binding protein (see the entire document, the Abstract in particular).

Therefore, the Ting et al., P11021, Witzmann et al., and Haas et al. references anticipate the claimed invention.

18. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Hsu et al., of record.

Hsu et al. teach recombinant BiP, which is a recombinant immunoglobulin heavy chain binding protein (see the entire document). Hsu et al. further teach that BiP is a member of the family of hsp70 heat shock proteins which recognize exposed, extended regions of polypeptide containing a large number of hydrophobic residues (see page 595, right column, final paragraph, and page 596, first 8 lines in particular).

Therefore, the Hsu et al. reference anticipates the claimed invention.

19. Claims 18, 22-23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Kozutsumi et al., of record.

Kozutsumi et al. teach cloning a recombinant GRP78, a recombinant immunoglobulin heavy chain binding protein, which was identified based upon homology with BiP in a pharmaceutical-suitable carrier (i.e. phosphate buffered saline and complete/incomplete Freund's adjuvant; see the entire document, page 118 in particular). Claims 22, 23, and 25 are included because the intended use of the pharmaceutical composition is not given patentable weight.

Therefore, the Kozutsumi et al. reference anticipates the claimed invention.

20. Claims 44, 48, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,188,964.

The '964 patent teaches heat shock proteins and a relationship between said heat shock proteins and glucose-related proteins (GRP's), and grp94 and grp78 are two major grp's (see column 2, lines 22-27 in particular). The '964 patent further teaches kits comprising Western Blot and ELISA assays comprising the immunoglobulin heavy chain binding proteins/stress-response proteins for detection and measurement of stress response proteins, such as grp94 (see claims 14-24 in particular).

Therefore, the '964 patent anticipates the claimed invention.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over 5,188,964.

The '964 patent has been discussed supra.

The '964 patent does not teach instructions for the use of the kit.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include instructions for the kit taught by the '964 patent for commercial use.

One of ordinary skill in the art would have been motivated to provide instructions for persons outside of the producing library to ascertain how to use the kit as taught by the '964 patent.

23. Claims 44, 45, 46, 49, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,188,964, in view of Hsu et al., of record, or Sambrook et al. (Molecular Cloning: A Laboratory Manual (1989) Cold Spring Harbor Laboratory Press, New York; page 17.2).

The '964 patent has been discussed supra.
The '964 patent does not teach recombinant immunoglobulin heavy chain binding proteins (grp).

Hsu et al. teach recombinant immunoglobulin heavy chain binding proteins (i.e. glucose-regulated protein, grp78) which are in the same family as hsp 70, both of which recognize exposed, extended regions of polypeptide containing a large number of hydrophobic residues (see page 595, the Abstract and right column, final paragraph, and page 596, first 8 lines in particular).

Sambrook et al. teach "methods for expressing large amounts of protein from a cloned gene (i.e. recombinant) introduced into *Escherichia coli* have proven invaluable in the purification, localization, and functional analysis of proteins" (see page 17.2, first 3 lines in particular). Further, high levels of protein are produced, purification is relatively easy, and proteins produced are biologically active (see entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made that the recombinant grp's taught by Hsu et al. or the recombinant technology taught by Sambrook et al. could be substituted for the non-recombinant grp's taught by the '964 patent as Western and ELISA blots are generic and any protein (recombinant or otherwise) can be tested. Claim 45 is included because it would be obvious to include instructions for a commercial product to be sold commercially.

One of ordinary skill in the art would have been motivated to substitute the recombinant proteins taught by Hsu et al. and Sambrook et al. in the Western and ELISA blots taught by the '964 patent because the assays were used to detect and measure the recombinant proteins as taught by the '964 patent.

24. Claims 22-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,348,945 in view of Hsu et al., of record.

The '945 patent teaches hsp70 in a pharmaceutical composition (see column 2, lines 53-56 in particular).

The '945 patent does not specifically teach a recombinant immunoglobulin heavy chain binding protein.

Hsu et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant immunoglobulin heavy chain binding protein taught by Hsu et al. for the hsp70 taught by the '945 patent. Claims 22-23 and 25 are included because the intended use of the composition is not given patentable weight.

One of ordinary skill in the art would have been motivated to substitute the recombinant protein because both the recombinant immunoglobulin heavy chain binding protein taught by Hsu et al. and the hsp70 taught by the '945 patent belong to the same family of proteins and bind proteins with the same structural features as taught by Hsu et al.

25. Applicant is notified that SEQ ID NOS: 1 and 2 are free of the prior art.

26. Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Margaret (Megan) Jamroz, Ph.D.
Patent Examiner
Technology Center 1600
February 6, 2002

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640